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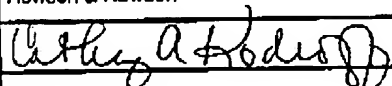
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TRANSMITTAL FORM <i>(to be used for all correspondence after initial filing)</i>	Application Number	10/601,442	
	Filing Date	8/23/2003	
	First Named Inventor	Fensome et al.	
	Art Unit	1614	
	Examiner Name	D. Jones	
Total Number of Pages in This Submission	20	Attorney Docket Number	AHPWA22AUSA

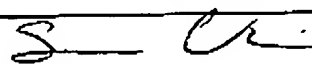
**Certificate
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of Correction**

ENCLOSURES (Check all that apply)		
<input type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Reply to Missing Parts/Incomplete Application <input type="checkbox"/> Reply to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation <input type="checkbox"/> Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____ <input type="checkbox"/> Landscape Table on CD	<input type="checkbox"/> After Allowance Communication to TC <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input type="checkbox"/> Appeal Communication to TC (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below): Request for Certificate of Correction
Remarks _____ Customer No: 38199		

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Howson & Howson		
Signature			
Printed name	Cathy A. Kodroff		
Date	12-20-2006	Reg. No.	33,980

CERTIFICATE OF TRANSMISSION/MAILING

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This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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DEC 20 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 10/601,442 Confirmation No.: 7993
Applicant : Fensome et al.
Filed : June 23, 2003
Patent No. : 7,115,649
Issue Date : October 3, 2006
TC/Art Unit : 1614
Examiner : D. Jones
Customer No. : 38199
Title : METHODS OF TREATING SKIN DISORDERS USING
THIO-OXINDOLE DERIVATIVES

Attention: Certificate of Corrections Branch
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 35 USC SECTION 254

Sir:

The following errors were found in the above-identified patent.

1. Col. 3, Line 47, replace "NRC^COR^B;" with -- NR^CCOR^B; --.
2. Col. 6, Line 61, replace "Nor" with -- N or --.

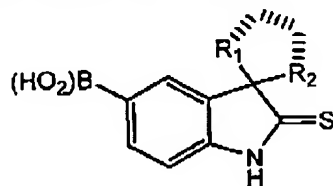
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UNDER 37 CFR 1.8

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Dated: Dec 20, 2006

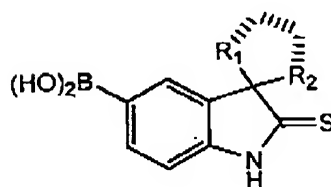
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3. Col. 14, Line 2, replace "optiQnally" with -- optionally --.
4. Col. 18, Scheme 4, replace the following structure:



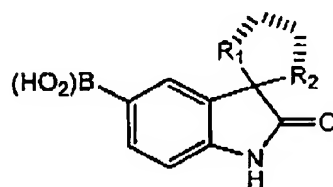
14

with the following structure:



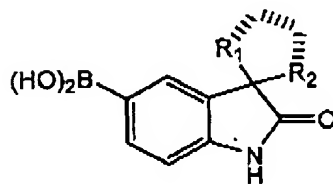
14

5. Col. 19, Scheme 5, replace the following structure:



14

with the following structure:



14

6. Col. 29, Line 16, replace "when'the" with -- when the --.
7. Col. 33, Line 29, replace "5-(5-Cyano-1-methyl-1H-pyrrol-2-yl)" with -- 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl) --.

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8. Col. 41, Line 3, replace "X" with -- X^2 --.
9. Col. 44, Line 65, replace "beterocyclic" with -- heterocyclic --.
10. Col. 45, Line 24, replace "C₃" with -- C₆ --.
11. Col. 45, Line 50, replace "aryl, substituted C₁" with
-- aryl, substituted aryl, C₁ --.
12. Col. 45, Line 57, replace "C₃ alkyl" with -- C₄ alkyl --.
13. Col. 46, Line 1, replace "c₁" with -- C₁ --.
14. Col. 46, Line 14, replace "C₃" with -- C₆ --.
15. Col. 46, Line 15, replace ", substituted C₃ to C₆" with
-- , substituted C₁ to C₆ --.
16. Col. 46, Line 50, replace "-CH₂(CH₂)₂CH₂-" with -- -CH₂(CH₂)_nCH₂-, --.
17. Col. 46, Line 64, replace "ospiro[cyclohekan-1,3-[3H]indol]-5'-yl)-2-" with
-- ospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2- --.
18. Col. 47, Line 1, replace "[3H]-indol]-5'-yl)-2-" with
-- [3H]-indol]-5-yl)-2- --.

It is requested that a Certificate of Correction be issued to correct the above errors in accordance with the enclosed forms, which are submitted herewith.

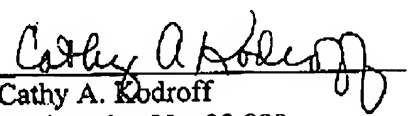
Because all errors were made by the US Patent and Trademark Office (USPTO), no fee is due for correction of these errors. To support Applicants' assertion that these are USPTO errors, Applicants have enclosed a copy of the original specification pages as filed which contain the correct language for errors (1) - (7) noted above. The correct language in these original specification pages is identified by a handwritten bolded box.

Errors (8) - (18) were also typographical errors in the claims on the part of the USPTO. To support this assertion, Applicants' have enclosed copies of the relevant pages of the Response filed on April 18, 2006 which contains the correct language for original claim 11, issued claim 12; original claim 23, issued claim 19; original claim 21; issued claim 21 and original claim 24, issued claim 23.

AHPWA22AUSA

The director of the US Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 08-3040.

Respectfully submitted,
HOWSON & HOWSON LLP
Attorneys for Applicant

By: 
Cathy A. Kodroff
Registration No. 33,980
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Fort Washington, PA 19034
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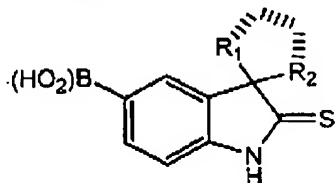
UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 3

PATENT NO. 7,115,649
APPLICATION NO. 10/601,442
ISSUE DATE. October 3, 2006
INVENTOR(S). Fensome et al.

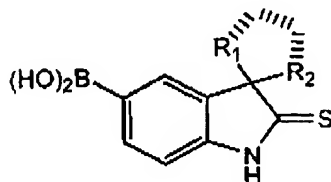
It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

1. Col. 3, Line 47, replace "NRC^COR^B," with -- NR^CCOR^B; --.
2. Col. 6, Line 61, replace "X¹ is Nor CX²;" with -- X¹ is N or CX²; --.
3. Col. 14, Line 2, replace "optiQnally" with -- optionally --.
4. Col. 18, Scheme 4, replace the following structure:



14

with the following structure:



14

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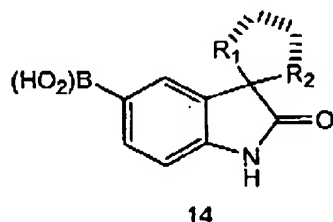
UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 2 of 3

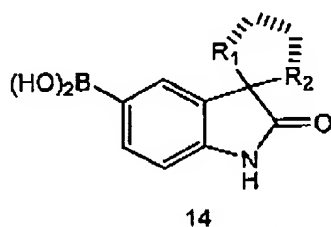
PATENT NO. 7,115,649
APPLICATION NO. 10/801,442
ISSUE DATE. October 3, 2006
INVENTOR(S). Fansome et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

5. Col. 19, Scheme 5, replace the following structure:



with the following structure:



6. Col. 29, Line 16, replace "when'the" with -- when the --.
7. Col. 33, Line 29, replace "5-(5-Cyano-1-methyl-1H-pyrrol-2-yl)" with --
5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl) --.

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Page 3 of 3

PATENT NO. 7,115,649
APPLICATION NO. 10/601,442
ISSUE DATE. October 3, 2006
INVENTOR(S). Fensome et al.

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9. Col. 44, Line 65, replace "beterocyclic" with -- heterocyclic --.
10. Col. 45, Line 24, replace " C_3 " with -- C_6 --.
11. Col. 45, Line 50, replace "aryl, substituted C_1 " with -- aryl, substituted aryl C_1 --.
12. Col. 45, Line 57, replace " C_3 alkyl" with -- C_4 alkyl --.
13. Col. 46, Line 1, replace " c_1 " with -- C_1 --.
14. Col. 46, Line 14, replace " C_3 " with -- C_6 --.
15. Col. 46, Line 15, replace ", substituted C_3 to C_6 " with -- , substituted C_1 to C_6 --.
16. Col. 46, Line 50, replace "- $CH_2(CH_2)_2CH_2$ -" with -- $-CH_2(CH_2)_nCH_2-$, --.
17. Col. 46, Line 64, replace "ospiro[cyclohekan-1,3-[3H]indol]-5'-yl)-2-" with -- ospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2- --.
18. Col. 47, Line 1, replace "[3H]-indol]-5'-yl)-2-" with -- [3H]-indol]-5-yl)-2- --.

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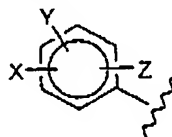
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- 5 -

R^5 is selected from the group consisting of a), b) and c):

a) a substituted benzene ring having the structure:



X is selected from the group consisting of halogen, OH, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkyl, substituted C_1 to C_3 thioalkyl, $S(O)alkyl$, $S(O)_2alkyl$, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2 , C_1 to C_3 perfluoroalkyl, substituted C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring comprising 1 to 3 heteroatoms, $CONH_2$, $CSNH_2$, $CNHNHOH$, CNH_2NOH , $CNHNHOH$, COR^B , CSR^B , $OCOR^B$, and $NR^C COR^B$;

R^B is selected from the group consisting of H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, and substituted C_1 to C_3 aminoalkyl;

R^C is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independently selected from the group consisting of H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 thioalkyl, and substituted C_1 to C_3 thioalkyl;

b) a five or six membered heterocyclic ring comprising 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 and having one or two independent substituents from the group consisting of H, halogen, CN, NO_2 , C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, COR^D , CSR^D , and $NR^E COR^D$;

R^D is H, NH_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

- 9 -

Y is selected from the group consisting of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, and C₁ to C₃ thioalkyl;

(ii) a five membered ring having the structure:



5 wherein:

U is O, S, or NR⁶;

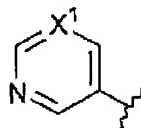
R⁶ is H, C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

X' is selected from the group consisting of halogen, CN, NO₂, CONH₂, CNHNHOH, CNH₂NOH, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂,

10 CSN(alkyl)₂, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

Y' is selected from the group consisting of H, F, and C₁ to C₄ alkyl; or

(iii) a six membered ring having the structure:



wherein:

15

X' is N or CX²;

X² is halogen, CN, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl,

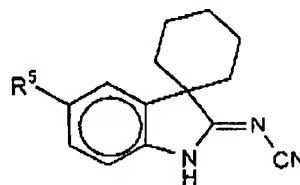
CON(alkyl)₂, CSN(alkyl)₂ or NO₂;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

Preferably, R⁵ is the five membered ring (ii) and U is O or S.

20

In yet another embodiment, the compound is of formula III:



III

- 20 -

point of attachment is through the oxygen-atom and the aryl group is optionally substituted.

The term "alkylcarbonyl" as used herein refers to the C(O)(alkyl) group, where the point of attachment is through the carbon-atom of the carbonyl moiety and the
5 alkyl group is optionally substituted.

The term "alkylcarboxy" as used herein refers to the C(O)O(alkyl) group, where the point of attachment is through the carbon-atom of the carboxy moiety and the alkyl group is optionally substituted.

The term "aminoalkyl" as used herein refers to both secondary and tertiary
10 amines where the point of attachment is through the nitrogen-atom and the alkyl groups are optionally substituted. The alkyl groups can be the same or different.

The term "halogen" as used herein refers to Cl, Br, F, or I groups.

The compounds of the present invention encompass tautomeric forms of the structures provided herein characterized by the bioactivity of the drawn structures.

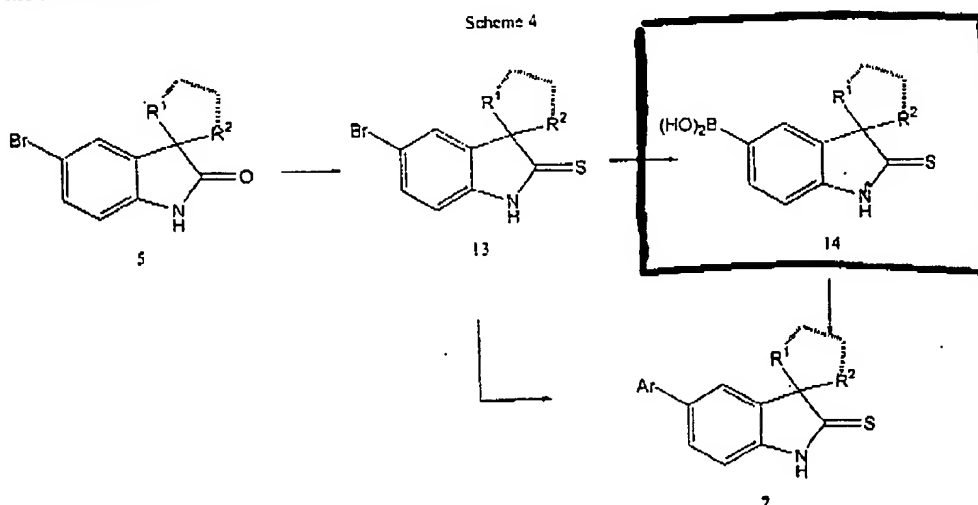
15 Further, the compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids, bases, alkali metals and alkaline earth metals.

Physiologically acceptable acids include those derived from inorganic and organic acids. A number of inorganic acids are known in the art and include
20 hydrochloric, hydrobromic, hydroiodic, sulfuric, nitric, and phosphoric acids, among others. Similarly, a variety of organic acids are known in the art and include, without limitation, formic, acetic, propionic, oxalic, succinic, glycolic, glucuronic, maleic, furoic, fumaric, citric, glutamic, benzoic, anthranilic, salicylic, phenylacetic, mandelic, embonic, methanesulfonic, ethanesulfonic, panthenoic, benzenesulfonic,
25 stearic, sulfanilic, alginic, and galacturonic acids, among others.

Physiologically acceptable bases include those derived from inorganic and organic bases. A number of inorganic bases are known in the art and include aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc sulfate or phosphate compounds, among others. A number of organic bases are known in the art

- 24 -

Reaction of the indoline-2-one derivative 6 with either Lawesson's reagent or phosphorous pentasulfide in a suitable organic solvent (pyridine, THF, dioxane, dimethoxyethane, dichloromethane, benzene, toluene, xylene) at a temperature between room temperature and the reflux temperature of the solvent provides access to the thiocarbonyl derivative 7. An additive such as sodium hydrogen carbonate can also be useful.

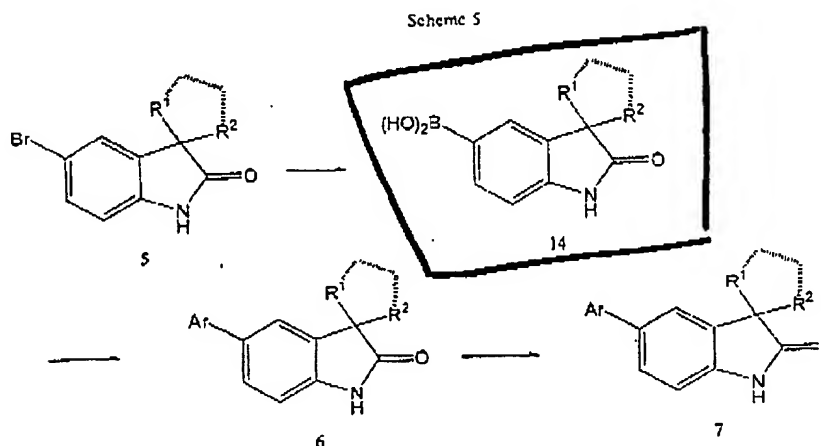


An alternative mode of preparation is to react compound 5 with either Lawesson's reagent or phosphorous pentasulfide in a suitable organic solvent (pyridine, THF, dioxane, dimethoxyethane, dichloromethane, benzene, toluene, xylene) at a temperature between room temperature and the reflux temperature of the solvent, under an inert atmosphere (nitrogen or argon) providing access to the thiocarbonyl derivative 13. The reaction of bromide 13 in an anhydrous solvent (e.g. THF, Et₂O) with a strong base (sodium hydride preferred, sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20 °C) with n-butyllithium and N,N,N,N'-tetramethylethylenediamine followed after a suitable period of time by a trialkylborate (trimethyl or triisopropylborate) gives after acidic work-up the boronic acid 14 (Scheme 4). Compound 14 can then be reacted under palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0) or palladium acetate, base (NaHCO₃,

- 25 -

Na_2CO_3 , K_2CO_3 , triethylamine, CsF) solvent (toluene/EtOH/water, THF/water, dimethoxyethane/water, anhydrous dimethoxyethane) with an aryl or heteroaryl bromide, aryl or heteroaryl iodide, aryl or heteroaryl trifluoromethane sulfonate or aryl or heteroaryl fluorosulfonate, to provide the desired compounds 7.

- 5 Alternatively reaction of compound 13 under palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0) or palladium acetate, base (NaHCO_3 , Na_2CO_3 , K_2CO_3 , triethylamine, CsF) solvent (acetone/water, toluene/EtOH/water, THF/water, dimethoxyethane/water, anhydrous dimethoxyethane) with an aryl or heteroaryl bromide, aryl or heteroaryl iodide, aryl or heteroaryl trifluoromethane sulfonate or aryl or heteroaryl fluorosulfonate, to provide the desired compound 7.
- 10



- 15 Treatment of the bromide 5 in an anhydrous solvent (e.g. THF, Et_2O) with a strong base (sodium hydride preferred, sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20°C) with *n*-butyllithium and $\text{N,N,N,N}'$ -tetramethylethylenediamine followed after a suitable period of time by a trialkylborate (trimethyl or triisopropylborate) gives after acidic work-up the boronic acid 15 (Scheme 5). Compound 15 can then be reacted under
- 20 palladium catalyzed conditions tetrakis(triphenylphosphine)palladium(0), base (NaHCO_3 , Na_2CO_3 , K_2CO_3 , triethylamine, CsF) solvent (toluene/EtOH/water,

- 37 -

European Patent No. 314,206, among others); hydrophobic membrane materials, such as ethylenemethacrylate (EMA) and ethylenevinylacetate (EVA); bioresorbable polymer systems (International Patent Publication No. WO 98/44964 and US Patent Nos. 5,756,127 and 5,854,388); and other bioresorbable implant devices composed of, for example, polyesters, polyanhydrides, or lactic acid/glycolic acid copolymers (US Patent No. 5,817,343). For use in such sustained delivery devices, the compounds of the invention can be formulated as described herein. See, US Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719.

In yet another embodiment, the compounds are topically delivered using a topical vehicle including creams, pastes, gels, ointments, lotions, liquids, solutions, suspensions, or foams or can be alone delivered prior or subsequent to the topical vehicle. Topical compositions can be applied to the area of the body which is afflicted with the skin disorder and includes the face, scalp, legs, arms, torso, or armpits. Preferably, the topical vehicles are anti-comedogenic.

Skin conditioning agents can include any reagent which provides a conditioning effect to the skin and/or does not clog the pores of the skin. A number of skin conditioning agents are known in the art and include, without limitation, skin conditioning agents that can be applied to the skin, including water-based lotions, creams, pastes, gels, ointments or foams.

The regimens of the invention can include the continuous delivery of the compounds of the invention. In another embodiment, the regimens can include the periodic discontinuation of delivery of the compounds of the invention. Such periodic discontinuation can include delivery of a placebo during the period of time where the compounds of the invention are not delivered to the patient. Alternatively, no placebo or active agent is delivered to the patient when the compounds are not being delivered to the patient.

By the term "placebo" or "inactive agent" is meant a reagent having pharmacological properties that are not relevant to the condition being treated, i.e.,

- 44 -

dose units of an estrogen; and, optionally, an orally and pharmaceutically acceptable placebo for each of the remaining 0 to 9 days in the 28-day cycle.

In a preferred embodiment, a 28-day kit can include a first phase of 21 daily dosage units of a compound of formula I; a second phase of 3 daily dosage units for
5 days 22 to 24 of an estrogen; and, optionally, a third phase of 4 daily units of an orally and pharmaceutically acceptable placebo for each of days 25 to 28.

Preferably, the daily dosage of each pharmaceutically active component of the regimen remain fixed in each particular phase in which it is delivered. It is further preferable that the daily dose units described are to be delivered in the order
10 described, with the first phase followed in order by the second and third phases. To help facilitate compliance with each regimen, it is also preferred that the kits contain the placebo described for the final days of the cycle.

A number of packages or kits are known in the art for the use in dispensing pharmaceutical agents for oral use. Preferably, the package has indicators for each
15 day of the 28-day cycle, and more preferably is a labeled blister package, dial dispenser package, or bottle.

The following examples are provided to illustrate the invention and do not limit the scope thereof. One skilled in the art will appreciate that although specific reagents and conditions are outlined in the following examples, modifications can be
20 made which are meant to be encompassed by the spirit and scope of the invention.

EXAMPLES

Example 1 – Treatment of Acne

25 A twenty-five year old human patient having acne vulgaris is treated according to the present invention. Specifically, 5'-(5-Cyano-1-methyl-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'-ylidenecyanamide is orally delivered to the patient daily. Delivery is in the form of a tablet formulated to contain about 20 mg of

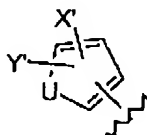
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wherein:

X is selected from the group consisting of halogen, CN, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂, CSN(alkyl)₂, CNHNHOH, CNH₂NOH, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring comprising 1 to 3 heteroatoms, and C₁ to C₃ thioalkyl;

Y is selected from the group consisting of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₄ alkyl, and C₁ to C₃ thioalkyl;

(ii) a five membered ring having the structure:



wherein:

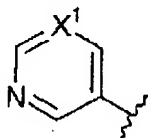
U is O, S, or NR⁶;

R⁶ is H, C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

X' is selected from the group consisting of halogen, CN, NO₂, CONH₂, CNHNHOH, CNH₂NOH, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂, CSN(alkyl)₂, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

Y' is selected from the group consisting of H, F, and C₁ to C₄ alkyl; or

(iii) a six membered ring having the structure:



wherein:

X¹ is N or CX²;

X² is halogen, CN, CONH₂, CSNH₂, CONHalkyl, CSNHalkyl, CON(alkyl)₂, CSN(alkyl)₂ or NO₂;

or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

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X^2 is halogen, CN, CONH_2 , CSNH_2 , CONHalkyl , CSNHalkyl , CON(alkyl)_2 , CSN(alkyl)_2 or NO_2 ;
or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

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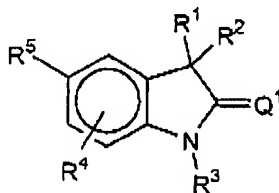
20(Previously Presented). The method according to claim 22, wherein:
 R^1 and R^2 are alkyl or substituted alkyl;
 R^3 is H.

21(Previously Presented). The method according to claim 22, wherein:
 R^1 and R^2 are joined to form a ring selected from the group consisting of
-CH₂(CH₂)_nCH₂-, -CH₂CH₂C(CH₃)₂CH₂CH₂-, -O(CH₂)_mCH₂-, -O(CH₂)_pO-,
-CH₂CH₂OCH₂CH₂-, -CH₂CH₂N(H)CH₂CH₂-, and -CH₂CH₂N(alkyl)CH₂CH₂-;
 R^3 is H.

22(Previously Presented). The method according to claim 22, wherein:
 R^3 is H;
 Q^1 is S or NR^7 .

23(Previously Presented). A method of conditioning the skin comprising the step of delivering to a mammal in need thereof a composition comprising:

- (i) a skin conditioning component; and
- (ii) a compound of formula I, or a tautomer thereof:



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wherein:

R^1 and R^2 are selected from the group consisting of H, alkyl, substituted alkyl, OH, O(alkyl), O(substituted alkyl), O(Acetyl), aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, alkylaryl, substituted alkylaryl, alkylheteroaryl, substituted alkylheteroaryl, 1-propynyl, substituted 1-propynyl, 3-propynyl, and substituted 3-propynyl;

or R^1 and R^2 are joined to form a ring selected from the group consisting of $-\text{CH}_2(\text{CH}_2)_n\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$, $-\text{O}(\text{CH}_2)_m\text{CH}_2-$, $-\text{O}(\text{CH}_2)_p\text{O}-$, $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{N}(\text{H})\text{CH}_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{N}(\text{alkyl})\text{CH}_2\text{CH}_2-$;

m is an integer from 1 to 4;

n is an integer from 1 to 5;

p is an integer from 1 to 4;

or R^1 and R^2 form a double bond to $\text{C}(\text{CH}_3)_2$, $\text{C}(\text{cycloalkyl})$, O, or $\text{C}(\text{cycloether})$;

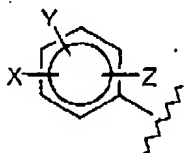
R^3 is selected from the group consisting of H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_3 to C_6 alkenyl, alkynyl, substituted alkynyl, and COR^A ;

R^A is selected from the group consisting of H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, and substituted C_1 to C_3 aminoalkyl;

R^4 is selected from the group consisting of H, halogen, CN, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, C_1 to C_6 aminoalkyl, and substituted C_1 to C_6 aminoalkyl;

R^5 is selected from the group consisting of a), b) and c):

a) a substituted benzene ring having the structure:



X is selected from the group consisting of halogen, OH, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3

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thioalkyl, substituted C_1 to C_3 thioalkyl, $S(O)alkyl$, $S(O)_2alkyl$, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2 , C_1 to C_3 perfluoroalkyl, substituted C_1 to C_3 perfluoroalkyl, 5 or 6 membered heterocyclic ring comprising 1 to 3 heteroatoms, $CONH_2$, $CSNH_2$, $CNHNHOH$, CNH_2NOH , $CNHNHOH$, COR^B , CSR^B , $OCOR^B$, and $NR^C COR^B$;

R^B is selected from the group consisting of H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, and substituted C_1 to C_3 aminoalkyl;

R^C is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

Y and Z are independently selected from the group consisting of H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 thioalkyl, and substituted C_1 to C_3 thioalkyl;

b) a five or six membered heterocyclic ring comprising 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 and having one or two independent substituents from the group consisting of H, halogen, CN, NO_2 , C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, COR^D , CSR^D , and $NR^E COR^D$;

R^D is H, NH_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

R^E is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^6 is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, or C_1 to $C_4 CO_2 alkyl$; or

c) an indol-4-yl, indol-7-yl or benzo-2-thiophene moiety, wherein said moiety is optionally substituted by from 1 to 3 substituents selected from the group consisting of halogen, alkyl, substituted alkyl, CN, NO_2 , alkoxy, substituted alkoxy, and CF_3 ;

Q^1 is S, NR^7 , or $CR^8 R^9$;

R^7 is selected from the group consisting of CN, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl,

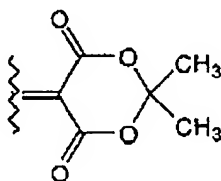
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heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, SO_2CF_3 , OR^{11} , and $\text{NR}^{11}\text{R}^{12}$;

R^8 and R^9 are independent substituents selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, NO_2 , CN, and CO_2R^{10} ;

R^{10} is C_1 to C_3 alkyl or substituted C_1 to C_3 alkyl;

or CR^8R^9 comprise a six membered ring having the structure:



R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclic ring, substituted heterocyclic ring, acyl, substituted acyl, aroyl, substituted aroyl, sulfonyl, and substituted sulfonyl; or a pharmaceutically acceptable salt, tautomer, metabolite, or prodrug thereof.

24(Previously Presented). The method according to claim 23 wherein said compound of formula I is selected from the group consisting of 5'-(3-Chlorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-thione, 3-(1',2'-Dihydro-2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)benzonitrile, 4-1',2'-Dihydro-2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2'-thiophenecarbonitrile, 3-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-5-fluorobenzonitrile, 4-Methyl-5-(1,2-dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-2'-thiophenethioamide, 5-(1,2-Dihydro-2-thioxospiro[cyclopentane-1,3-[3H]indol]-5'-yl)-1H-pyrrole-2-carbonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-1-(tert-butoxycarbonyl)-pyrrole-2-carbonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-1-H-pyrrole-2-carbonitrile, 5-(2'-thioxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1-methylpyrrole-2-carbonitrile, 5-(1,2-Dihydro-2-thioxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-